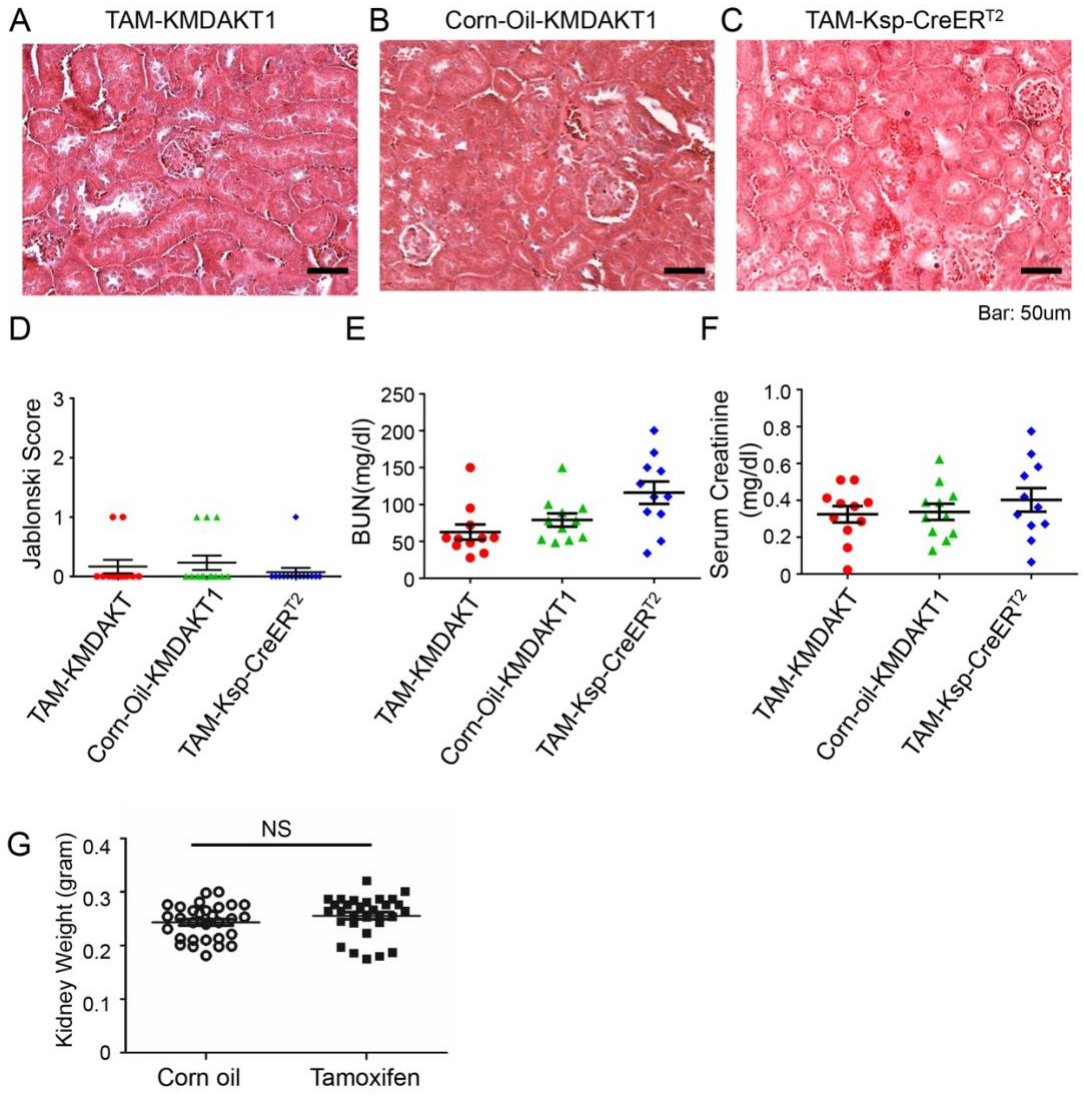
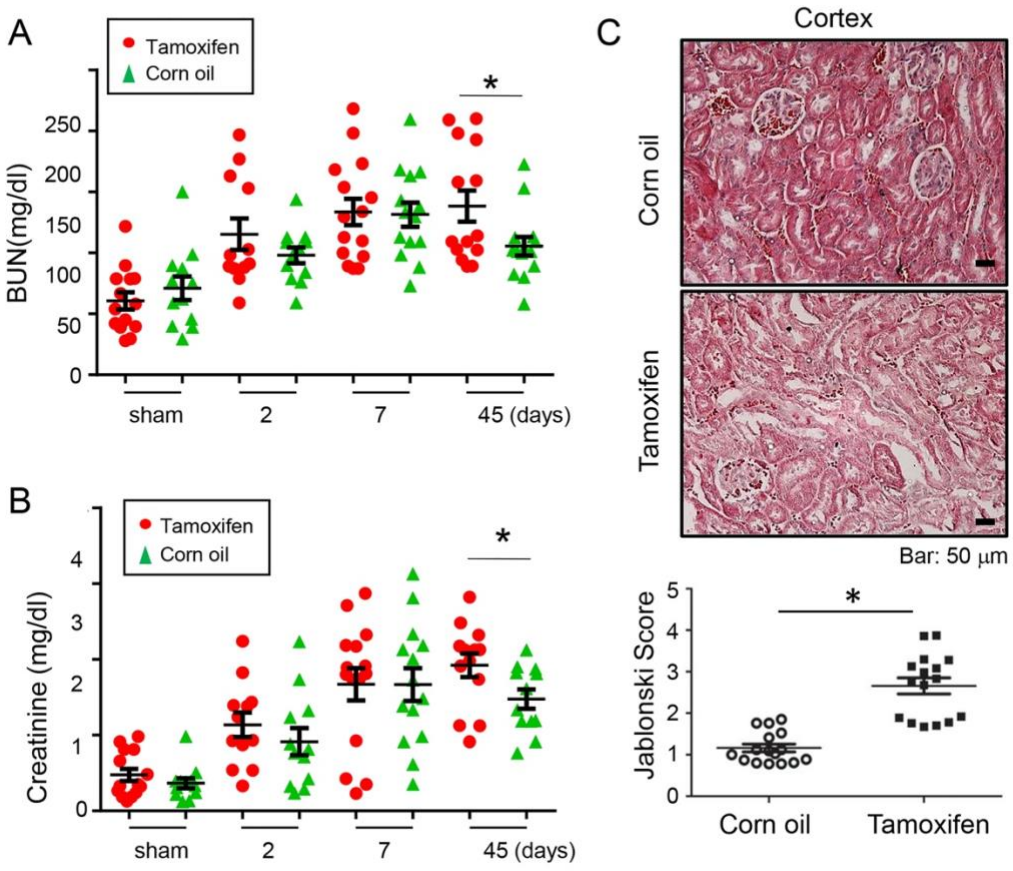
Supplemental Figure 1



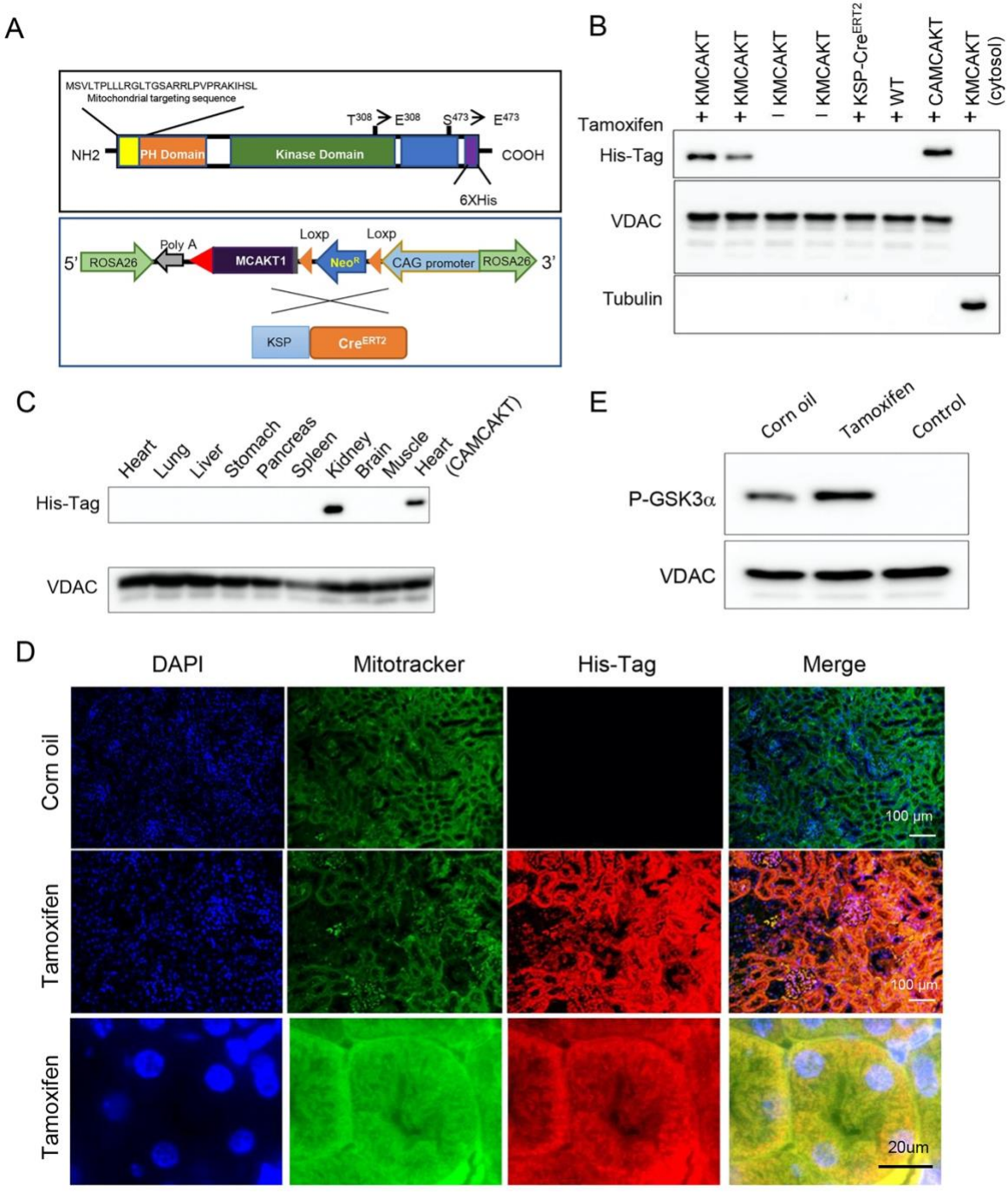
Supplemental Figure 1. Tamoxifen did not change baseline renal histology or renal function in KMDAKT Mice. One month after TAM injection, kidney was harvested and fixed. Kidney sections were analyzed with hematoxylin and eosin (HE) staining. There was no significant morphological difference among kidney samples from (A) TAM-KMDAKT mice, (B) corn oil-KMDAKT mice and (C) TAM-KSP-CreER^{T2} mice. (D) There was no difference in Jablonski scores among 3 groups of animals. Serum was collected at the time of euthanization and (E) BUN and (F) Cr were measured. Cr and BUN did not differ among the three groups (all male). (G) Weight of kidneys in KMDAKT mice. NS: not significant.

Supplemental Figure 2



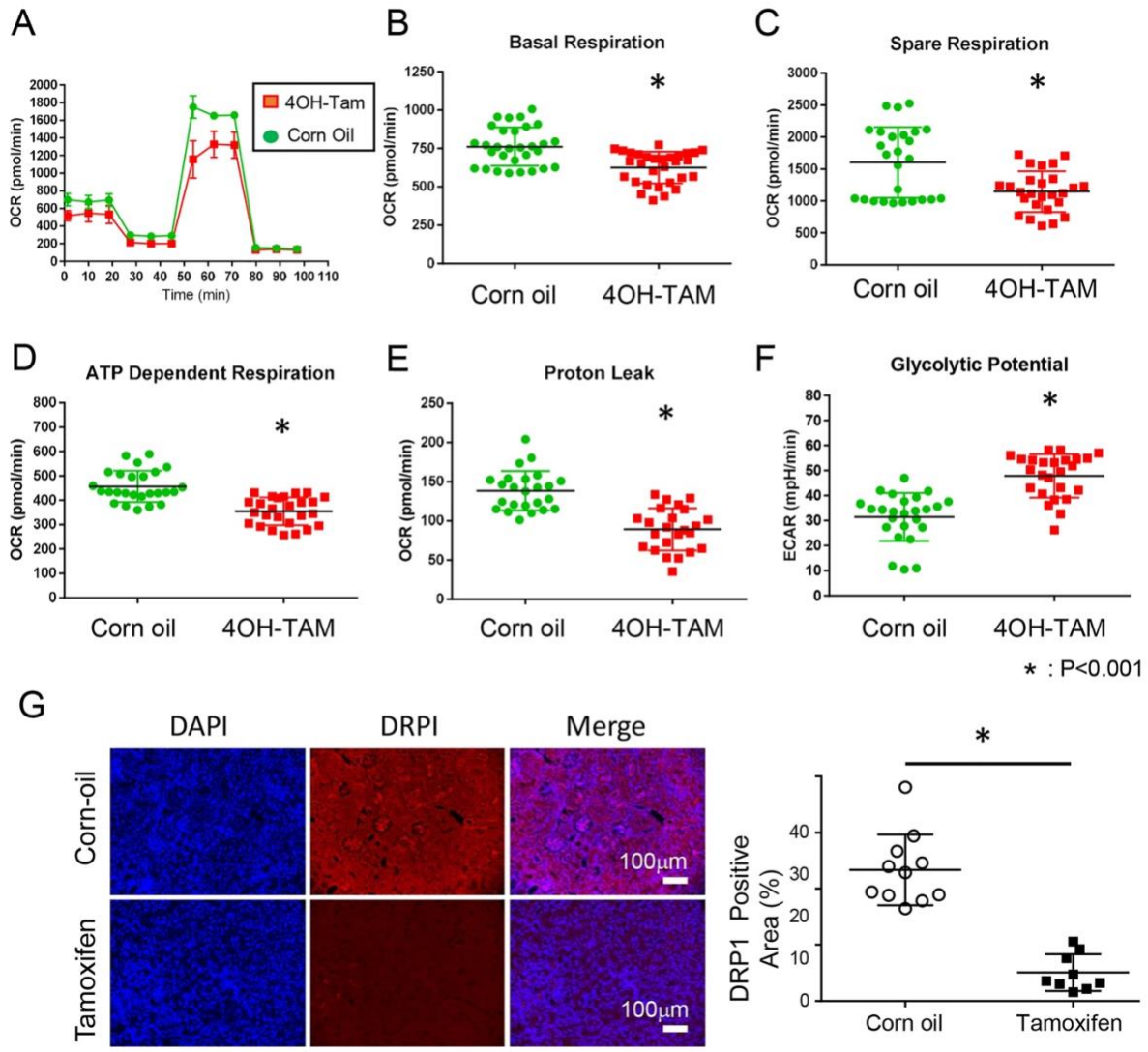
Supplemental Figure 2. Inhibition of tubule mitochondria AKT aggravated renal function induced by IRI in female mice. The effect of ischemia-reperfusion in female KMDAKT mice was studied with the same protocol as in male mice. (A, B) Serial measurements showed higher BUN and Cr after IRI in the female Tam-KMDAKT mice on day 45 (n=11-13 in each group, *$p < 0.04$). (C) Tubular injury and Jablonski scores. *$p<0.02$.

Supplemental Figure 3



Supplemental Figure 3. Bigenic mice (KMCAKT) for renal tubule-specific mitochondria-targeting of a constitutively active AKT1. (A) Mitochondrial-targeted constitutively active AKT1 (mcaAKT) was engineered as described in Materials and Methods. A 6X His tag was fused in frame to the C terminus of AKT1 cDNA. mcaAKT transgenic mice were crossed with KSP/CreER^{T2} mice to generate bi-transgenic mice (KMCAKT) for this series of experiments. (B) Eight-week-old KMCAKT mice were injected with TAM or corn oil. The mitochondrial fraction was isolated and expression of mcaAKT proteins was analyzed by western blot. The mcaAKT protein was expressed in the renal mitochondria isolated from Tam-KMDAKT mice but not in corn oil-KMCAKT mice, TAM-KSP/CreER^{T2} mice or TAM-wildtype (WT) mice. A heart-specific CMCAKT mice served as a positive control for the mutant AKT after TAM injection. No mcaAKT was present in the renal cytosolic fraction (last lane). VDAC was used as loading control and mitochondrial marker, while tubulin was used as a cytosolic marker. (C) After TAM injection, mitochondrial fraction was isolated from different organs, mutant AKT was only expressed in the kidney, confirming kidney specificity. The mcaAKT proteins in the cardiac mitochondria of TAM-injected heart-specific CAMCAKT mice served as a positive control. (D) Mutant AKT1 co-localized with mitochondria in the renal tubules, immunofluorescence staining was carried out with anti-His-Tag antibody and MitoTracker® Green FM. (E) The mitochondrial AKT activity was analyzed by in vitro kinase assay using recombinant GSK3α as substrate. AKT activity was increased in the Tam-KMCAKT mitochondria. The control was from the supernatant of KMCAKT mitochondria proteins after clearing immunoprecipitation with AKT antibodies (negative control).

Supplemental Figure 4



Supplemental Figure 4. Activation of mitochondrial AKT improved mitochondrial respiration in renal tubular epithelial cells.

(A) Primary renal tubule epithelial cells (RTE) were isolated from 3-week-old KMCAKT mice and treated with DMSO or 10ng/ml of tamoxifen (4-OH TAM) for transgene induction. Mitochondria respiration was analyzed with a Seahorse XF Analyzer. Different inhibitors were injected sequentially to measure different stages of respiration (complex V inhibitor: oligomycin, uncoupler: FCCP, and complex I inhibitor: Rotenone) as shown in B-F. * p<0.001. (G) DRP1 staining in KMCAKT kidneys. Mitochondrial fission marker DRP1 was analyzed with immunofluorescence. The bar graph summarized the results from each group. * p< 0.001.

Supplemental Materials

Phospho-AKT1 (Ser473) Antibodies (＃9271) and His-Tag (D3I1O) XP® (＃12698) Cleaved Caspase 3 (#9579), Cleaved Caspase 9 (#9509), and Drp1 (#8570), P-GSK-3α (#9331) were purchased from Cell Signaling Technology (Danvers, MA). AKT1 antibodies (E45) (ab32038) were purchased from Abcam (Cambridge, UK). VDAC and Anti-Aquaporin 1 (AB2219) antibodies were from Millipore Sigma (Burlington, MA). MitoTracker®Green FM (M7514), MitoTracker®Red 580 FM (M22425), Alexa Fluor® 555 (A31572) and Alexa Fluor®488 (A11013) secondary antibodies were purchased from Invitrogen (Carlsbad, CA). KIM-1 (＃AF1817) antibodies were purchased from R&D Systems (Minneapolis, MN). The QuantiChrom Urea Assay Kit and QuantiChrom Creatinine Assay Kit were purchased from BioAssay Systems (Hayward, CA). Chemicals and reagents were from Sigma Aldrich (St Louis, MO).

Supplemental Methods

Transgenic Mice

In brief, for mitochondrial-targeting (mt-targeting) sequence from human cytochrome c oxidase subunit 8A (NP_004065.1; MSVLTPLLLRGLTGSARRLPVPRAKIHSL) was added to the 5’ end of the AKT1 cDNA. The mt-targeting sequence is removed during mitochondrial import. To generate a dominant-negative AKT1 (mdnAKT), K179 was mutated to methionine to abolish ATP binding. To generate a constitutively active AKT (mcaAKT), threonine T308 and serine S473 were mutated to glutamic acid to mimic

phosphorylation. To mediate cre-conditional expression of mcaAKT and mdnAKT in mice, each coding sequence was first cloned into pCALNL-dsRed[S1]; pCALNL-DsRed was a gift from Dr. Constance Cepko (Addgene plasmid # 13769) following removal of the Ds-Red coding sequence.

In pCALNL[S2,S3] a CMV immediate early gene enhancer and chicken beta-actin gene promoter/intron and beta-globin polyA signal drives expression of a coding sequence following cre-mediated deletion of a floxed PGK-neo-polyA sequence between the promoter and the coding sequence.[S4] To mediate targeting to the ROSA26 (Gt(ROSA)26Sor) locus, mcaAKT and mdnAKT were independently cloned into pROSA26-1, a gift from Dr. Philippe Soriano (Addgene plasmid # 21714)[S4] with the CAG promoter oriented opposed to the ROSA26 lnc RNA transcript.

JM8.N4 ES cells (derived from C57BL/6NTac mice)[S5] were electroporated with linearized targeting constructs and 32 G418-resistant clones for each construct were screened for homologous recombination. Targeting efficiency was 50% for the mdnAKT construct and 53% for the mcaAKT construct. Correctly targeted ES cells were microinjected into C57BL/6J blastocysts and the resulting male chimeras were bred with C57BL/6 mice to establish the lines used in this study. Engineering of mES cells, genomic characterization, microinjection of blastocysts and production of founder transgenic mice were carried out at the UCI Transgenic Mouse Facility.

To mediate inducible overexpression of mdnAKT or mcaAKT in the renal tubule epithelial cells, ROSA26-CAG-LNL-mdnAKT or ROSA26-CAG-LNL-mcaAKT mice were crossed with a well-studied Cre transgenic mouse strain, KSP-CreER^{T2} mice[59]; Tg(Cdh16-

cre/ERT2)24Igr) that were on a congenic C57BL/6 background (gift from Dr. Peter Igarashi, UT Southwestern Medical Center, TX)[59], to generate KMDAKT or KMCAKT mice. Mice were kept in a temperature-controlled environment, and fed ad libitum with laboratory chow (2020X, Envigo Teklad, UK). To induce AKT1 transgene expression, 8-week-old KMDAKT heterozygous, KSP-CreER^{T2} hemizygous or KMCAKT heterozygous, KSP-CreER^{T2} and control mice were treated with Tamoxifen (TAM), 100 mg/kg body weight/day i.p. for 5 days. Expression of transgene was verified 4 weeks afterwards. One month after initial tamoxifen or corn oil injection, the mice were subject to acute kidney injury as described below. The experimental protocol was approved by the Institutional Animal Care and Use Committee at the University of California at Irvine (AUP-18-113) and the experiments were performed in accordance with federal and local guidelines.

Serum BUN and Creatinine

To analyze serum BUN and Creatinine level, blood was collected from the retro-orbital plexus under anesthesia 7 days after IRI. Serum was obtained by centrifugation at 10,000 x g for 30 min at room temperature. BUN or Creatinine levels were determined with colorimetric assay kits according to the manufacturer's instructions (BioAssay Systems, Hayward, CA) with a plate reader (Biotek Synergy HT).

Hematoxylin and Eosin (HE) Stain and Tubular Injury

Kidney samples were collected 7 days after IRI and fixed overnight in 10% buffered formalin at 4°C, washed twice with phosphate-buffered saline (PBS), incubated in 65% and 70% ethanol, and progressively dehydrated with graded ethanol and Histoclear

(National Diagnostics) with a Leica TP1020 tissue processor, and embedded in paraffin. After deparaffinization and rehydration, the tissue sections (4 um) were stained with Mayer's hematoxylin solution (Sigma-Aldrich, MO) for 15 minutes, rinsed with running tap water for 2 minutes, and stained with bluing solution (0.1% sodium bicarbonate) for 5 minutes. The slides were counter-stained with Eosin solution for 20 seconds, dehydrated with graded ethanol/xylene and mounted. Images were captured with a Zeiss AxioPlan2 microscope and analyzed with AxioVision Rel 4.6 software or with a Keyence BZ-X810 Inverted Microscope (Keyence, Osaka, Japan) and analyzed with Keyence BZ-X800 Analyzer software.

At least 20 random images from each slide were used for histopathology analysis. The investigators who scored the histology images were blinded to the samples. Renal damage in proximal tubules from cortex area and outer stripe of outer medulla (OSOM) of the kidney were evaluated with semi-quantitative analysis of histological damage areas with Jablonski grading scale for the assessment of overall proximal tubule injury [54]. Approximately one hundred tubules were scored in each section and the total scores divided by the number of tubules analyzed. The following criteria were used for scoring. 0: normal or no tubular injury. 1: areas of tubular epithelial cell swelling, vacuolar degeneration, necrosis and desquamation involving <25% of the tubular profile. 2: similar changes involving >25% but <50% of the tubular profile. 3: similar changes involving >50% but <75% of the tubular profile. 4: similar changes involving>75% of the tubular profile.[S6]

Masson's Trichrome Stain

Masson's trichrome staining was performed to evaluate renal fibrosis 7 days after IRI. Briefly, 4 mm paraffin sections were deparaffinized in xylene and rehydrated in graded ethanol. The sections were mordant in Bouin's solution (picric acid, formaldehyde, and acetic acid) overnight. After washing, they were stained with Weigert's Iron Hematoxyline Solution for 30 minutes, followed by Biebrich Scarlet-Acid Fucshin for 15 minutes, phosphomolybdic-phosphotungstic acid solution for 10 minutes, and then aniline blue for 20 minutes. After brief submersion in 0.5% acetic acid, the slides were dehydrated with 95% alcohol, 100% alcohol, and xylene. Images were captured with a Zeiss AxioPlan2 microscope and analyzed with AxioVision Rel 4.6 software or with a Keyence BZ-X810 Inverted Microscope (Keyence, Osaka, Japan) and analyzed with Keyence BZ-X800 Analyzer software. Blue coloration of collagens in the extracellular matrix (ECM), was digitally calculated with ImageJ, ECM contents were quantified as mean blue intensity per tissue area.

Immunohistochemistry

For the immunohistochemistry analysis, 4 um renal sections were deparaffinized, rehydrated, and pretreated with 3% H_2O_2 before permeabilized with 0.01% Triton X100 in PBS, antigen unmasking was performed in 0.05% saponin in ddH_2O at room temperature for 30 minutes. For activated caspase 3 and 9 staining, kidney sections were treated with 3% H_2O_2 and then 0.1M Tris (pH10) at 95^{o}C for 10 minutes. After cooling to room temperature, the sections were treated with 0.05% saponin in ddH_2O. After washing three times with PBS, the sections were incubated with 4% bovine serum albumin (BSA) in PBS for 30 minutes before reacting with primary antibodies at 4 °C overnight.

The slides were washed with PBS three times and incubated with biotinylated secondary antibodies for 45 minutes at room temperature, rinsed with PBS three times, and Avidin-conjugated-Horseradish peroxidase (HRP) (VECTASTAIN ABC kit, Vector Lab, Burlingame, CA) for 30 minutes. Staining was visualized with a solution containing 3, 3–diaminobenzidine (Sigma-Aldrich, St Louis, MO), and counter-stained with 1% methyl green for nuclei. KIM-1 was used as a marker for renal tubular injury.[S7] 20 microscopic fields were randomly selected from each tissue section, recorded with a Zeiss AxioPlan2 microscope, and analyzed with AxioVision Rel 4.6 software, or with a Keyence BZ-X810 Inverted Microscope (Keyence, Osaka, Japan).

Immunofluorescence

Paraffin-embedded kidney sections were deparaffinized with xylene and rehydrated with graded ethanol. For antigen retrieval, the slides were immersed in 0.1M Tris (pH 10) buffer and heated with a 1100 W GE microwave oven for three 3-min cycles at power levels of 5, 4 and 3. After cooling, the slides were rinsed with PBS. The tissue sections were circled with a liquid Blocker Super Pap Pen before applying primary antibodies (diluted in 1XPBS, 4% BSA, 0.1% Triton X-100) and incubated overnight in a humified chamber at 4°C.

After extended washes with PBS, fluorescence-conjugated secondary antibodies were applied and placed in a humidified chamber, incubated in a GE microwave oven at power level 4 for 3 minutes, rinsed with PBS and stained with Mitotracker (10 nM) and DAPI (1

ug/ml) for 20 minutes at room temperature. After washing with PBS, the slides were mounted for analysis with Keyence BZ-X810 Inverted Microscope (Keyence, Osaka, Japan).

For primary renal epithelial cells, the cells were plated onto 12 mm cover glasses the day before staining. Cells were fixed with 3.7% formaldehyde in PBS with 0.1% Triton X100 at room temperature for 30 minutes. After three washes with PBS, the cells were permeabilized with 0.05% saponin in ddH_2O for 20 minutes, washed three times with PBS, blocked with 10% goat serum in PBS for 30 minutes, incubated with primary antibodies at 4°C overnight, washed three times, and reacted with Alexa Fluor®488 conjugated secondary antibodies for 30 minutes. The slides were counterstained with DAPI and Mitotracker (10nM) when indicated and analyzed with a Keyence BZ-X810 Inverted Microscope.

Mitochondria Preparation

7 days after IRI, renal cortical and outer medulla tissues were isolated from the kidney, minced, washed with ice-cold PBS 3 times, and suspended in a mitochondria isolation buffer (20 mM HEPES-KOH, pH 7.2, 10 mM KCl, 1.5 mM $MgCl_2$, 1.0 mM EDTA, 1.0 mM EGTA, 1.0 mM dithiothreitol, 2 mM phenylmethylsulfonyl fluoride, 20 mM NaF, 2 mM Na_3VO_4, and 250 mM sucrose). The samples were incubated on ice for 30 min and homogenized with 20 strokes of loose pestle and 50 strokes of tight pestle in a Dounce homogenizer. The nuclei and cell debris were removed by centrifugation at 1,000Xg for 15 minutes at 4°C. The supernatants were centrifuged at 10,000X g for 4°C for 30 minutes, and the resulting mitochondrial fractions were re-suspended with mitochondria

isolation buffer. The supernatants were further centrifuged at 100,000X g at 4°C for 1 hour. The cytosolic fraction and mitochondrial fraction were stored at -80°C when indicated.

Western Blot Analysis

The mitochondrial fractions were dissolved in 2% lauryl maltoside solution supplemented with 10% SigmaFAST™ protease inhibitor (Sigma-Aldrich, S8820). Equal amounts of proteins from each sample were resolved with 10% SDS-polyacrylamide gel and transferred onto polyvinylidene difluoride membranes. The membranes were blocked with 5% fat-free milk or 5% BSA for one hour at room temperature before incubation with primary antibodies overnight at 4℃. After three washes with TBS-T (20mM Tris–HCl, pH7.5, 0.5 mM NaCl, and 0.1% Tween 20), the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (1:2000 dilution in 5% fat-free milk or 5% BSA) for 1 hour at room temperature. After three washes, the membranes were developed with West Pico Chemiluminescent Substrate (Thermo Scientific, Pittsburgh, PA) and the images were acquired with a Syngene G:BOX and analyzed with ImageJ.

TUNEL Stain

Kidney sections were deparaffinized and incubated with 0.05% saponin at room temperature for antigen unmasking. To detect apoptosis of renal cells, renal sections were stained with the In Situ Cell Death Detection Kit according to the manufacturer's instructions (Roche, Indianapolis, IN). At the end of the staining, the slides were

counterstained with 1% Methyl Green and the images were acquired with a Zeiss AxioPlan2 microscope or with a Keyence BZ-X810 Inverted Microscope. At least 20 microscopic fields were randomly selected from each tissue section and TUNEL-positive nuclei were analyzed with ImageJ for quantitative analysis.

AKT Activity Assay

To study the activity of AKT in mitochondria, mitochondria preparations were isolated as described above and AKT enzymatic activity was analyzed with an AKT Assay Kit (#ab65786) (Abcam, Cambridge, UK) according to the manufacturer's instructions. In brief, AKT was immunoprecipitated from the solubilized mitochondria preparations and the enzymatic activities were quantitated with recombinant GSK-3α proteins. Phosphorylation of GSK-3α was visualized with western blots.

Primary Culture of Renal Epithelial (RTE) Cells

Kidneys were harvested from mice under anesthesia. After removing renal capsules and medulla, kidneys were minced into small pieces and resuspended in sterile PBS. After passing the buffer through a 70-μm filter (VWR® Cell Strainers, #10199-656), the primary RTE cells were incubated in DMEM/F12 supplemented with 25mM HEPES, 0.1 mM nonessential amino acids, 2 mM glutamate, 0.1 mM 2-mercaptoethanol and 7.5% fetal bovine sera. To induce transgene expression, primary RTE cells were incubated with 4 hydroxytamoxifen (4OH-TAM) at a final concentration of 10 ng/ml for 24 hours.

ATP Measurement, Mitochondria Respiration and Lipid Peroxidation

The levels of ATP in the RTE cells was determined by the ATP Detection Assay Kit (#700410) (Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. To analyze mitochondria function, we used a Seahorse Bioscience XF24 Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA) to analyze specific stages of respiration with a protocol modified from our previous study (11). RTE cells were plated in a 0.2% gelatin coated 24-well Seahorse XF-24 assay plate at 10^5 cells/well and grown for 16 hours before analysis. On the day of analysis, cells were washed once with freshly prepared unbuffered DMEM/F12 media without serum and incubated in this media at 37°C in a non-CO2 incubator for 1 hr. Three baseline measurements of oxygen consumption rate (OCR) were taken before sequential injection of following mitochondrial inhibitors (final concentration): oligomycin (1 µg/ml), carbonilcyanide p-triflouromethoxyphenylhydrazone (FCCP) (3 µM) and rotenone (0.1 µM). Three measurements were taken after addition of each inhibitor. The data were calculated and recorded by the Seahorse XF-24 software. The basal respiration was calculated by averaging the three measurements of (OCR) before injection of inhibitors. Kidney malondialdehyde was measured as a marker of lipid peroxidation using a Lipid Peroxidation Assay Kit from Abcam (ab118970) (Abcam, Cambridge, UK) according to the manufacturer's specification.

Total RNA Isolation

5-6 20mm paraffin sections were collected and placed in a microtube from each block (the first 4 sections were discarded). The paraffin was removed by 3 washes of 1ml Xylene (50oC) for 3 min and following by 2 washes of 100% ethanol, The tissue sections

were then air dried for 1 min before 150ml of FFPE buffer (20mM Tris-HCl (pH8.0), 1mM CaCl2, 0.5% SDS) with fresh protease K (500 mg/ml) were added to each sample and incubated at 55oC overnight. After, the samples were heat at 80oC for at least 15 min to reverse the cross-linking generated by formaldehyde. 1ml of Trizol was added to each sample and incubated at room temperature for at least 5 minutes before 0.2ml of chloroform was added. After vigorously vortexing the tube for 15 sec, the sample was incubated at 15-30oC for 2-3 min before centrifugation at no more than 12,000Xg for 15 min at 4oC. After transferring the aqueous phase to a fresh tube, 10ug glycogen and 0.6ml isopropyl alcohol were added and RNA was precipitated at -20oC for at least 1 hr. The RNA pellet was collected by centrifugation at 12,000Xg for 10 min at 4oC. After washing with 70% ethanol, the RNA pellet was briefly air dried before dissolved in RNase-free water.

Real Time Quantitative PCR

RNA was reverse transcribed into cDNA using an iScript gDNA Clear cDNA Synthesis Kit (#1708891) (Bio-Rad, Hercules, CA) according to the manufacturer's protocol. Quantitative RT-PCR was performed using Apex qPCR GREEN Master Mix (#42-119PG) (Genesee Scientific, San Diego, CA). 300ng of DNA was used as input in a 10uL total reaction volume on a LifeTechnologies QuantStudio 6 RT-PCR instrument (LifeTechnologies, Carlsbad, CA). The qPCR program consisted of an initial activation at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1min. GAPDH was used as an endogenous control for normalization. GAPDH: (forward: 5′-catcactgccacccagaagactg -3′; reverse: 5′-atgccagtgagcttcccgttcag-3′), TGB-β: (forward: 5′-ctcccgtggcttctagtgc-3′; reverse: 5′-gccttagtttggacaggatctg-3′), Col1a: (forward: 5′-

gctcctcttaggggccact-3′; reverse: 5′-ccacgttctaccattgggg-3′), aSMA: (forward: 5′-accatcggcaatgagcgtttcc-3′; reverse: 5′-gctgttgtaggtggtctcatgg-3′).

Mitochondria DNA Content

For DNA extraction, tissue section collection and paraffin removal was similar to the RNA preparation described above. After paraffin removal, the collected tissue was incubated with 500 ml of digestion buffer (10 mM Tris-HCl pH 8.0, 100 mM EDTA pH 8.0, 50 mM NaCl, 0.5% SDS) with freshly added 200 mg/ml (final concentration) proteinase K at 56oC for 48 hours, followed by 15 min of incubation at 80oC. The DNA were cleaned with Phenol/Chloroform extraction and precipitated with ethanol. The clean DNA were used for mitochondrial copy number analysis by real-time PCR. Quantitative PCR was performed using Apex qPCR GREEN Master Mix (#42-119PG)

(Genesee Scientific, San Diego, CA). 5ng of DNA was used as input in a 20uL total reaction volume on a LifeTechnologies QuantStudio 6 RT-PCR instrument (LifeTechnologies, Carlsbad, CA). The qPCR program consisted of an initial activation at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1min. Beta-Globin was used as a nuclear DNA control for normalization. COX-II:(forward: 5′-gccgactaaatcaagcaaca-3′; reverse: 5′-caatgggcataaagctatgg-3′), β-globin: (forward: 5′-gaagcgattctagggagcag-3′; reverse: 5′-ggagcagcgattctgagtaga-3′).

Supplemental References

S1. Gilbert RE. Proximal Tubulopathy: Prime Mover and Key Therapeutic Target in Diabetic Kidney Disease. Diabetes. 2017;66(4):791-800.

S2. Matsuda T, Cepko CL. Controlled expression of transgenes introduced by in vivo electroporation. Proc Natl Acad Sci USA. 2007;104(3):1027-32.

S3. Kanegae Y, Lee G, Sato Y, et al. Efficient gene activation in mammalian cells by using recombinant adenovirus expressing site-specific Cre recombinase. Nucleic Acids Res. 1995;23(19):3816-21.

S4. Soriano P. Generalized lacZ expression with the ROSA26 Cre reporter strain. Nat Genet. 1999;21(1):70-1.

S5. Pettitt SJ, Liang Q, Rairdan XY, et al. Agouti C57BL/6N embryonic stem cells for mouse genetic resources. Nat Methods. 2009;6(7):493-5.

S6. Patel V, Li L, Cobo-stark P, et al. Acute kidney injury and aberrant planar cell polarity induce cyst formation in mice lacking renal cilia. Hum Mol Genet. 2008;17(11):1578-90.

S7. Ferenbach, D.A, Bonventre J.V, Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol, 2015;11(5):264-76